A_1 ADENOSINE RECEPTOR ANTAGONISTS

Related Applications

This application claims the benefit of United States provisional patent application Serial No. 60/448,212, filed February 19, 2003, the disclosure of which is incorporated by reference herein in its entirety.

Field of the Invention

The present invention concerns compounds useful as A_1 adenosine receptor antagonists, along with methods of use thereof.

Background of the Invention

Adenosine receptors are involved in a vast number of peripheral and central regulatory mechanisms such as, for example, vasodilation, cardiac depression, inhibition of lipolysis, inhibition of insulin release and potentiation of glucagon release in the pancreas, and inhibition of neurotransmitter release from nerve endings.

In general, adenosine receptors can be divided into two main classes, A_1 receptors which can inhibit, and A_2 receptors which can stimulate adenylate cyclase activity. One of the best known classes of adenosine receptor antagonists are the xanthines which include caffeine and theophylline. See e.g., Müller et al., *J. Med. Chem.* 33: 2822-2828 (1990). In general, many of these antagonists often suffer from poor water solubility, and low potency or lack of selectivity for adenosine receptors. Additionally, selective analogues of adenosine receptor antagonists have been developed through the "functionalized congener" approach. Analogues of adenosine receptor ligands bearing functionalized chains have been synthesized and attached covalently to various organic moieties such as amines and peptides. Attachment of the polar groups to xanthine congeners has been found to increase water solubility. Nonetheless, such developments

have yet to fully address problems associated with potency and selectivity. More recently Jacobson et al. *J. Med. Chem.* 35: 408-422 (1992) has proposed various derivatives of adenosine and theophylline for use as receptor antagonists. The article discloses that hydrophobic substituents are able to potentially enhance affinity. However, it is also acknowledged that such substituents may result in a decrease in solubility thus rendering the antagonists less soluble *in vivo*. In confronting these problems, Jacobson et al. indicates that a dipropyl substitution at the 1 and 3 positions of theophylline allows desirable affinity at A_1 receptors. It is also stated that substitutions at the 7-position are typically not favorable.

Selective analogues of adenosine receptor antagonists have been developed through the "functionalized congener" approach. See e.g., U.S. Patent No. 4,968,672 to Jacobson et al.; and Jacobson et al., *Mol. Pharmacol.* 29: 126-133 (1985). In terms of pharmacology, the compounds advantageously display increased affinity at A_1 receptor sites relative to former A_1 receptor antagonists while simultaneously exhibiting good water solubility.

U.S. Patent No. 5,786,360 to Neely describes A_1 adenosine receptor antagonists.

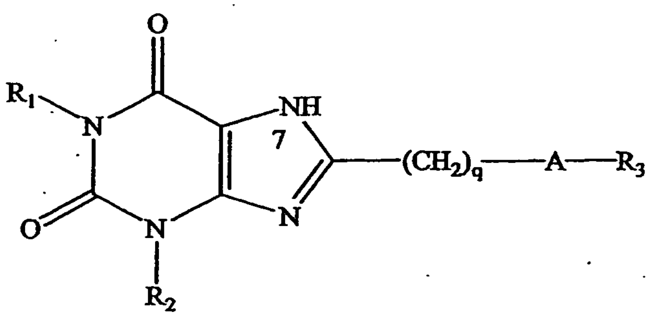
U.S. Patent No. 6,489,332 to Neely describes A_1 adenosine receptor antagonists.

U.S. Patent No. 5,719,279 to Kufner-Muhl et al. describes certain xanthine derivatives that have A_1 adenosine receptor affinity.

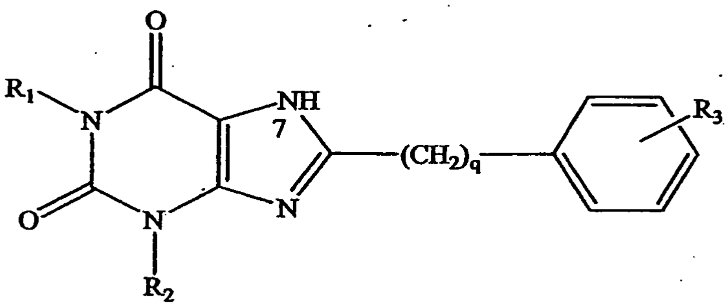
It is an object of the present invention to provide additional compounds useful as A_1 adenosine receptor antagonists, preferably compounds with good water solubility.

Summary of the Invention

In one aspect, the present invention provides a compound of the general formula (I) or (more particularly) formula (II):



(I)



(II)

wherein:

A is a 5 or 6 membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O and S;

R_1 and/or R_2 are water-soluble groups or other groups as described below;

R_3 is selected from the group consisting of H, NH_2, $R_{15}COOH$, wherein R_{15} is an alkyl or alkylidene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; halides such as chloro, bromo, iodo or fluoro, substituted amines such as NHR_8, NR_8R_9, substituted amides such as $NHCOR_8$, and NR_8COR_9 as well as water-solubilizing groups SO_3H and PO_3H_2; and

q is an integer ranging from 1 to 8, preferably 1 to 5, and most preferably 1 to 3.

In a second aspect, the invention provides for assay-type probes of the above compound, wherein the probes are marked or conjugated with a detectable group such as a radioactive or non-radioactive detectable group.

In a third aspect, the invention provides a pharmaceutically acceptable salt of the above compound.

In a fourth aspect, the invention provides a pharmaceutical composition which comprises the above compound or its pharmaceutically acceptable salt in combination with a pharmaceutically acceptable carrier.

A further aspect of the present invention is a method of treating A1-adenosine receptor related disorders, AIDS and immune deficiency disorders, asthma, other inflammatory medical conditions and still other medical conditions in a subject in need thereof, comprising administering a compound as described herein (*e.g.*, by inhalation or oral administration) to said subject in an amount effective to treat the said condition.

In a further aspect, the present invention provides for the use of compounds as described above for the preparation of a medicament for treating a disease in which antagonism of the A_1 adenosine receptor produces the desired effect.

Compounds of the present invention may further be used as described in C. Wilson, PCT Application WO 03/103675 (published December 18, 2003).

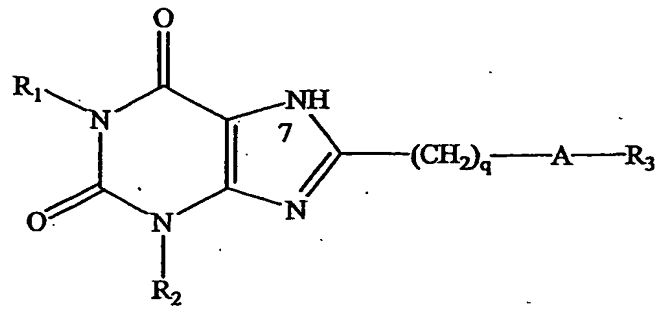
Detailed Description of the Preferred Embodiments

The present invention will now be described more fully hereinafter, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

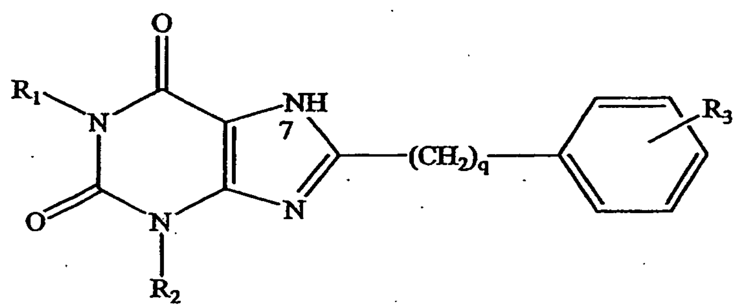
While the present invention is intended primarily for the treatment of human subjects, it will be appreciated that other subjects, particularly mammalian subjects such as dogs, cats, horses, rabbits, etc., can also be treated by the methods of the present invention for veterinary purposes.

"Halogen" as used herein refers to any suitable halo group, such as fluorine, chlorine, bromine, and iodine.

As noted above, the present invention is directed to a compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof:



(I)



(II)

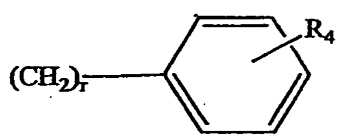
wherein:

A is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O and S;

R_1 is a water-soluble group as set forth below (or H, or in some embodiments is C_1-C_8 alkyl); and

R_2 is of the formula (i) or (ii):

$(CH_2)_r$—A'—R_4 (i)



(ii)

wherein:

A' is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O and S;

r is an integer ranging from 1 to 20; preferably 2 to 12 and most preferably 2 to 10 or in an alternate embodiment R_2 is a water-soluble group as defined below;

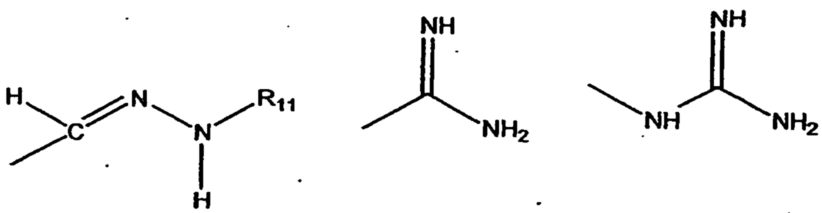
R_4 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; $R_{14}COOH$, wherein R_{14} is an alkyl or alkylidene group having 1 to 8 carbon atoms; halides such as chloro, bromo, iodo or fluoro, substituted amines such as NHR_8, NR_8R_9, substituted amides such as $NHCOR_8$, and NR_8COR_9 as well as water-solubilizing groups SO_3H and PO_3H_2; and

R_3 is selected from the group consisting of H, NH_2, $R_{15}COOH$, wherein R_{15} is an alkyl or alkylidene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; halides such as chloro, bromo, iodo or fluoro, substituted amines such as NHR_8, NR_8R_9, substituted amides such as $NHCOR_8$, and NR_8COR_9 as well as water-solubilizing groups SO_3H and PO_3H_2.

q is an integer ranging from 1 to 8, preferably 1 to 5, and most preferably 1 to 3.

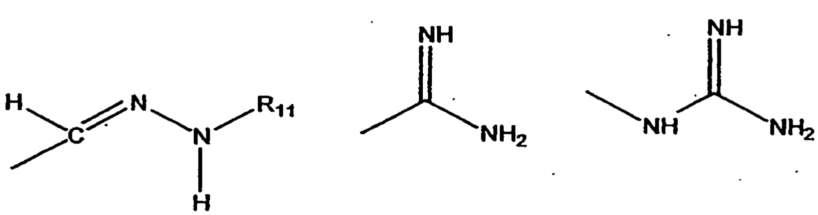
As noted above, R_1 and/or R_2 may be water-soluble groups or other groups in which R_1 and/or R_2:

denote a C_1-C_8 alkanyl group, C_2-C_8 alkenyl group or C_2-C_8 alkynyl group which is optionally substituted by -CN, $-CH_2NR_6R_7OH$ (multiple substitution also being possible), $-OR_8$, $-NR_6R_7$, $-NHCOR_8$, $-NHCONR_6R_7$, halogen, $-OCOR_8$, $-OCH_2COOH$, $-OCH_2COOR_8$, $-SO_2R_5$, $-S-R_5$, -NHCONH phenyl, $-OCH_2-CONR_6R_7$, $-OCH_2CH_2OH$, $-SO_2-CH_2-CH_2-O-COR_8$, $-OCH_2-CH_2-NR_6R_7$, $-SO_2-CH_2-CH_2-OH$, $-CONHSO_2R_8$, $-CH_2CONHSO_2R_8$, $-OCH_2CH_2OR_8$, -COOH, $-COOR_8$, $-CONR_6R_7$, -CHO, $-SR_8$, $-SOR_8$, $-SO_2R_8$, $-SO_3H$, $-SO_2NR_6R_7$, $-OCH_2-CH_2OCOR_8$, -CH=NOH, $-CH=NOR_8$, $-COR_9$, $-CH(OH)R_9$, $-CH(OR_8)_2$, $-CH=CH-R_{10}$, $-OCONR_6R_7$, $-PO_3H_2$,



or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted, preferably mono- substituted, by methyl; or

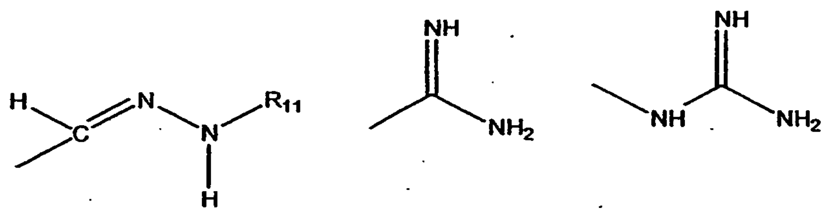
denote phenyl-C_1-C_6-alkylene, preferably phenyl-C_1-C_4-alkylene, phenyl-C_2-C_6-alkenylene or phenyl-C_2-C_6-alkynylene, in which the phenyl ring is optionally substituted, either directly or via a C_1-C_4-alkylene group, with one or more, preferably one, of the following groups, -C_1-C_3-alkyl, -CN, -$CH_2NR_6R_7$, -NO_2, -OH, -OR_8, -CH_2-NH-SO_2-R_8, -$NHCOR_8$, -$NHCONR_6R_7$, halogen, -$OCOR_8$, -OCH_2COOH, -OCH_2COOR_8, -CH_2OCOR_8, -SO_2R_5, -OCH_2-$CONR_6R_7$, -OCH_2CH_2OH, -OCH_2-CH_2-NR_6R_7, -$CONHSO_2R_8$, -$OCH_2CH_2OR_8$, -COOH, -$COOR_8$, -CF_3, cyclopropyl, -$CONR_6R_7$, -CH_2OH, -CH_2OR_8, -CHO, -SR_8, --SOR_8, -SO_2R_8, -SO_3H, -PO_3H_2, -$SO_2NR_6R_7$, -OCH_2-CH_2OCOR_8, -CH=NOH, -CH=NOR_8, -COR_9, -CH(OH)R_9, -CH$(OR_8)_2$, -$NHCOOR_8$, -$CH_2CONHSO_2R_8$, -CH=CH-R_{10}, -$OCONR_6R_7$, -CH_2-O-$CONR_6R_7$, -CH_2-CH_2-O-$CONR_6R_7$,



or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted, preferably monosubstituted, by methyl; or

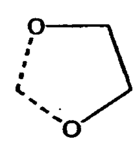
denote C_3-C_7-cycloalkyl-C_1-C_6-alkylene-, C_3-C_7-cycloalkyl-C_2-C_6-alkenylene-, C_3-C_7 -cycloalkyl-C_2-C_6-alkynylene-, in which the cycloalkyl group may optionally be substituted, either directly or via a C_{1-4}-alkylene group, by -CN, -$CH_2NR_6R_7$, =O, -OH, -

OR_8, $-NR_6R_7$, $-NHCOR_8$, $-NHCONR_6R_7$, halogen, $-OCOR_8$, $-OCH_2COOH$, $-OCH_2COOR_8$, $-CH_2OCOR_8$, $-SO_2R_5$, $-OCH_2CONR_6R_7$, $-OCH_2CH_2OH$, $-OCH_2-CH_2-NR_6R_7$, $-OCH_2CH_2OR_8$, $-COOH$, $-COOR_8$, $-CONR_6R_7$, $-CH_2OH$, $-CH_2OR_8$, $-CHO$, $-SR_8$, $-SOR_8$, $-SO_2R_8$, $-SO_3H$, $-PO_3H_2$, $-SO_2NR_6R_7$, $-OCH_2-CH_2-OCOR_8$, $-CH{=}NOH$, $-CH{=}NOR_8$, $-COR_9$, $-CH(OH)R_9$, $-CONHSO_2R_8$, $-CH(OR_8)_2$, $-NHCOOR_8$, $-CH{=}CH-R_{10}$, $-OCONR_6R_7$, $-CH_2-O-CONR_6R_77$, $-CH_2-CH_2-O-CONR_6R_7$, .



or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted, preferably monosubstituted, by methyl; or

denote a group of the formula A-C_1-C_6-alkylene-, A-CONH-C_1-C_6-alkylene-, A-CONH-C_2 –C_6-alkenylene-, A-CONH-C_2-C_6-alkynylene-, A-NH-CO-C_1-C_6-alkylene, A-NH-CO-C_2-C_6-alkenylene, A-NH-CO-C_2-C_6 alkynylene, A-C_2-C_6-alkenylene- or A-C_2 –C_6-alkynylene, wherein A is a C- or N-linked 5- or 6-membered heterocyclic ring, 5- or 6- membered aromatic ring, or 5-or 6- membered heteroaromatic ring which contains nitrogen, oxygen or sulphur as heteroatoms and may optionally be mono- or polysubstituted, preferably monosubstituted, by C_1-C_4-alkyl, halogen, $-OR_8$, -CN, $-NO_2$, $-NH_2$, $-CH_2NR_6R_7$, -OH, =O, a ketal, -COOH, $-SO_3H$, $-PO_3H_2$, $-COOR_8$, $-CONR_6R_7$, $-COR_9$, $-SO_2-R_8$, $-CONR_6R_7$ or



R_5 denotes C_1-C_4-alkyl, optionally substituted by OH, $OCOR_8$, NH_2, NR_6R_7 or $NHCOR_8$, and R_5 preferably represents $-CH_2$-CH_2-OH, $-CH_2CH_2OCOR_8$, $-CH_2$-CH_2-CH_2-OH; $-CH_2$-$CH_2CH_2OCOR_8$;

R_6 denotes hydrogen, an optionally substituted C_3–C_6-cycloalkyl group, a branched or unbranched alkyl-, alkenyl- or alkynyl group having up to 10 carbon atoms, preferably a C_1-C_8-alkyl group, which may optionally be substituted by hydroxy, phenyl, substituted phenyl, amino, substituted amino, C_1 to C_8, preferably C_1 to C_4-alkoxy, or it denotes $-(CH_2)_m$—$NHCOOR_8$ wherein m=1, 2, 3 or 4;

R_7 denotes hydrogen, an optionally substituted C_3–C_6-cycloalkyl group, a branched or unbranched alkyl-, alkenyl- or alkynyl group having up to 10, preferably 1-4, carbon atoms, which may optionally be substituted by hydroxy, phenyl, substituted phenyl, amino, substituted amino, C_1 to C_8, preferably C_1 to C_4-alkoxy, or it denotes –$(CH_2)_m$-$NHCOOR_8$ wherein m=1, 2, 3 or 4; preferably hydrogen, or R_6 and R_7 together with the nitrogen atom form a saturated or unsaturated 5- or 6-membered ring which may contain as heteroatoms nitrogen, oxygen or sulphur, while the heterocyclic ring may be substituted by a branched or unbranched C_1- to C_4-alkyl group, preferably methyl, or may carry one of the following groups: $-(CH_2)_n$-NH_2, =O, a ketal-preferably -O-CH_2-CH_2-O-, $-(CH_2)_n$.NH-C_1-C_4-alkyl, $-(CH_2)_n$-N(C_1-C_8-alkyl), $-(CH_2)_n$-$NHCOOR_8$, (n=2, 3, 4,), halogen, -OR_8, -CN, $-NO_2$, -NH_2, -$CH_2NR_6R_7$, -OH, -COOH, -SO_3H, -PO_3H_2, -$COOR_8$, -$CONR_6R_7$, -SO_2R_8,

R_8 denotes hydrogen, C_1-C_8-alkyl or C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted with CO_2H, a benzyl- or phenyl- group, which is optionally mono- or polysubstituted by OCH_3;

R_9 denotes C_1-C_8-alkyl or C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted with CO_2H, optionally substituted phenyl, optionally substituted benzyl, C_3-C_6-cycloalkyl, and

R_{10} denotes $-COOR_8$, -CH_2OR_8, -$CONR_6R_7$, hydrogen, C_1-C_3-alkyl, optionally substituted phenyl, $-CH_2NR_6R_7$.

Examples of 5- or 6-membered aromatic or heteroaromatic rings containing 0 to 4 heteroatoms selected from the group consisting of N, O and S include, but are not limited to those compounds shown in the Examples or named below.

Compounds as described above may be prepared in accordance with the techniques known in the art such as described in US Patent No. 5,719,279 to Kufner-Muhl et al., US Patent No. 5,786,360 to Neely, US Patent No. 6,489,332 to Neely, the techniques described in the Examples below, and variations of the foregoing that will be obvious to those skilled in the art of synthetic organic chemistry in light of the disclosure herein. Specific examples of compounds of the present invention that can be prepared by such techniques include but are not limited to:

3-[2-(4-acetaminophenyl)ethyl]-8-benzyl-1-butylxanthine;
3-[2-(2-acetaminophenyl)ethyl]-8-benzyl-1-pentylxanthine;
3-[2-(4-acetaminophenyl)ethyl]-8-benzyl-1-hexylxanthine;
3-[2-(4-acetaminophenyl)ethyl]-8-benzyl-1-propylxanthine;
3-[2-(4-acetaminophenyl)ethyl]-8-(3-chlorobenzyl)-1-propylxanthine;
3-[2-(3-acetaminophenyl)ethyl]-1-propyl-8-[(pyrimidin-5-yl)methyl]xanthine;
3-[2-(3-acetaminophenyl)ethyl]-8-[(1,3,4-oxadiazol-5-yl)methyl]-1-propylxanthine;
3-[2-(4-acetaminophenyl)ethyl]-1-propyl-8-(3-sulfonoxybenzyl)xanthine;
3-[2-(4-acetaminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine;
8-(3-aminobenzyl)-1-pentyl-3-(2-phenylethyl)xanthine;
8-(3-aminobenzyl)-3-(2-phenylethyl)-1-propylxanthine;
8-(2-aminobenzyl)-3-[2-(2-aminophenyl)ethyl]-1-propylxanthine;
8-(3-aminobenzyl)-3-[2-(3-aminophenyl)ethyl]-1-propylxanthine;
3-[2-[2-(6-aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;
3-[2-[3-(6-aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;
3-[2-[2-(6-aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine;
3-[2-[3-(6-aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine;
3-[2-(2-aminophenyl)ethyl]-8-benzyl-1-(3-dimethylaminopropyl)xanthine;
3-[2-(3-aminophenyl)ethyl]-8-benzyl-1-(3-dimethylaminopropyl)xanthine;
3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-(8-sulfonoxyoctyl)xanthine;
3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-(5-sulfonoxypentyl)xanthine;
3-[2-(2-aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;
3-[2-(3-aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;
3-[2-(2-aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine;
3-[2-(3-aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine;
3-[2-(4-aminophenyl)ethyl]-8-(4-fluorobenzyl-1-(3-sulfonoxypropyl)xanthine;
3-[2-(3-aminophenyl)ethyl]-1-butyl-8-[(pyridazin-4-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-butyl-8-[(pyridazin-4-yl)methyl]xanthine;
3-[2-(4-amino-3-chlorophenyl)ethyl]-1-propyl-8-[(pyridazin-4-yl)methyl]xanthine;

3-[2-(4-amino-2-chlorophenyl)ethyl]-1-propyl-8-[(1*H*-pyrrol-3-yl)methyl]xanthine;
3-[2-(4-amino-2-fluorophenyl)ethyl]-1-propyl-8-[(1*H*-pyrrol-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(1*H*-1,3,4-triazol-5-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-1-propyl-8-[(1*H*-1,2,4-triazol-5-yl)methyl]xanthine;
3-[2-(3-aminophenyl)ethyl]-8-[(1,2,4-oxadiazol-5-yl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(4-pyridyl)methyl]xanthine N-oxide;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(oxazol-2-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(isoxazol-4-yl)methyl]-1-propylxanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(5-chloroisoxazol-4-yl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-8-(2,4-difluorobenzyl)-1-propylxanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(5-fluoroisoxazol-4-yl)methyl]-1-pentylxanthine;
3-[2-(4-aminophenyl)ethyl]-8-[(4-fluoro-2-oxazolyl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-8-[(5-fluoro-2-oxazolyl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-8-[(isothiazol-3-yl)methyl]-1-propyl-xanthine;
3-[2-(3-aminophenyl)ethyl]-1-propyl-8-[(pyrimidin-2-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(4-fluoro-3-isothiazolyl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-8-[(5-fluoropyrimidin-2-yl)methyl]-1-propylxanthine;
3-[2-(3-aminophenyl)ethyl]-8-[(1,3,4-oxadiazol-5-yl)methyl]-1-pentylxanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(1*H*-pyrazol-3-yl)methyl]xanthine;
3-[2-(3-aminophenyl)ethyl]-1-propyl-8-[(1*H*-pyrazol-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-pentyl-8-[(1*H*-pyrazol-3-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-1-propyl-8-[(pyrazin-2-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-1-butyl-8-[(3-fluoropyrazin-2-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(3-fluoropyrazin-2-yl)methyl]-1-pentylxanthine;
3-[2-(2-aminophenyl)ethyl]-8-[(3-fluoropyrazin-2-yl)methyl]-1-propylxanthine;
3-[2-(4-aminophenyl)ethyl]-1-pentyl-8-[(2-fluoro-1*H*-pyrazol-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(1*H*-pyrrol-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(pyridazin-4-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-1-yl)methyl]xanthine;
3-[2-(2-aminophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine;
3-[2-(3-aminophenyl)ethyl]-1-propyl-8-[(furan-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(furan-2-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(thiophen-3-yl)methyl]xanthine;
3-[2-(4-aminophenyl)ethyl]-1-propyl-8-(3-sulfonoxybenzyl)xanthine;
8-benzyl-3-[2-(3-aminophenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(3-aminophenyl)ethyl]-1-butylxanthine;
8-benzyl-3-[2-(4-aminophenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(4-carboxyphenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(3-chlorophenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(2,4-difluorophenyl)ethyl]-1-pentylxanthine;
8-benzyl-3-[2-(2,4-difluorophenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(3-nitrophenyl)ethyl]-1-propylxanthine ;
8-benzyl-3-[2-(isothiazol-3-yl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(thiazol-3-yl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(isoxazol-3-yl)ethyl]-1-propylxanthine;

8-benzyl-3-[2-(1,3,4-oxadiazol-5-yl)ethyl]-1-pentylxanthine;
8-benzyl-3-[2-(1,2,4-oxadiazol-5-yl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-(4-fluorophenyl)ethyl]-1-pentylxanthine;
8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine;
8-benzyl-3-[2-phenylethyl]-1-pentylxanthine;
8-benzyl-3-[2-phenylethyl]-1-propylxanthine;
8-benzyl-1-propyl-3-[4-(2-sulfonoxyphenyl)butyl]xanthine;
8-benzyl-1-propyl-3-[4-(3-sulfonoxyphenyl)butyl]xanthine;
8-benzyl-1-propyl-3-[2-(2-sulfonoxyphenyl)ethyl]xanthine;
8-benzyl-1-propyl-3-[2-(3-sulfonoxyphenyl)ethyl]xanthine;
3-[2-(4-bromophenyl)ethyl]-1-propyl-8-[(4-pyridyl)methyl]xanthine;
3-[2-(2-carboxyphenyl)ethyl]-8-(3-fluorobenzyl)-1-propylxanthine;
3-[2-(2-carboxyphenyl)ethyl]-8-(3-nitrobenzyl)-1-propylxanthine;
3-[2-(2-carboxyphenyl)ethyl]-1-propyl-8-[(2-pyridyl)methyl]xanthine;
3-[2-(2-carboxyphenyl)ethyl]-1-propyl-8-[(2-pyridyl)methyl]xanthine;
3-[2-(4-chlorophenyl)ethyl]-1-propyl-8-[(4-pyridyl)methyl]xanthine N-oxide;
3-[2-(2,4-diaminophenyl)ethyl]-8-[(5-fluoro-2-oxazolyl)methyl]-1-propylxanthine;
3-[2-(2.4-difluorophenyl)ethyl]-1-propyl-8-[(2-pyridyl)methyl]xanthine N-oxide;
3-[2-(4-fluorophenyl)ethyl]-1-propyl-8-[(2-pyridyl)methyl]xanthine N-oxide;
3-[2-(2-fluorophenyl)ethyl]-1-propyl-8-[(pyrazin-2-yl)methyl]xanthine;
3-[2-(3-fluorophenyl)ethyl]-8-[(1,3,4-oxadiazol-5-yl)methyl]-1-propylxanthine;
3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(1*H*-pyrazol-3-yl)methyl]xanthine;
3-[2-(3-nitrophenyl)ethyl]-8-[(1,3,4-oxadiazol-5-yl)methyl]-1-propyllxanthine;
3-[2-(2-nitrophenyl)ethyl]-1-propyl-8-[(1*H*-1,2,4-triazol-5-yl)methyl]xanthine;
3-[2-(2-nitrophenyl)ethyl]-8-[(4-fluoro-3-isothiazolyl)methyl]-1-propylxanthine;
3-[2-(3-nitrophenyl)ethyl]-1-propyl-8-[(pyridazin-4-yl)methyl]xanthine;
3-[2-(3-nitrophenyl)ethyl]-8-[(1,2,4-oxadiazol-5-yl)methyl]-1-propylxanthine;
3-(2-phenyl)ethyl-8-benzyl-1-(8-sulfonoxyoctyl)xanthine;
3-(2-phenyl)ethyl-8-benzyl-1-(5-sulfonoxypentyl)xanthine;
3-(2-phenylethyl)-1-propyl-8-[(2-fluoro-2-pyridyl)methyl]xanthine N-oxide;
3-(2-phenylethyl)-1-propyl-8-[(1,2,4-oxadiazol-3-yl)benzyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(1,3,4-oxadiazol-5-yl)benzyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(1*H*-pyrazol-3-yl)benzyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(2-pyridyl)methyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(3-pyridyl)methyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(4-pyridyl)methyl]xanthine;
3-(2-phenylethyl)-1-propyl-8-[(2-pyridyl)methyl]xanthine N-oxide;
3-(2-phenylethyl)-1-propyl-8-[(3-pyridyl)methyl]xanthine N-oxide;
3-(2-phenylethyl)-1-propyl-8-[(4-pyridyl)methyl]xanthine N-oxide;
3-(2-phenylethyl)-1-propyl-8-(3-sulfonoxybenzyl)xanthine;
3-(2-phenylethyl)-1-propyl-8-(4-sulfonoxybenzyl)xanthine;
and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

The compound of the present invention may form pharmaceutically acceptable salts with both organic and inorganic acid and bases. Examples of suitable acids for salt

formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, ascorbic, maleic, methanesulfonic, benzenesulfonic, p-toluenesulfonic and the like. Any of the amine acid addition salts may also be used. The salts are prepared by contacting the free base form of the compound with an appropriate amount of the desired acid in a manner known to one skilled in the art. Examples of suitable bases for salt formation are sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, calcium hydroxide, ammonia, organic amines, and the like. The salts may be prepared by contacting the free acid form of the compound with an appropriate amount of the desired base in a manner known to one skilled in the art.

Active compounds of the invention may be provided in the form of prodrugs. The term "prodrug" refers to compounds that are transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Prodrugs as Novel delivery Systems, Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated by reference herein. *See also* US Patent No. 6,680,299. Examples include a prodrug that is metabolized in vivo by a subject to an active drug having an activity of active compounds as described herein, wherein the prodrug is an ester of an alcohol or carboxylic acid group, if such a group is present in the compound; an acetal or ketal of an alcohol group, if such a group is present in the compound; an N-Mannich base or an imine of an amine group, if such a group is present in the compound; or a Schiff base, oxime, acetal, enol ester, oxazolidine, or thiazolidine of a carbonyl group, if such a group is present in the compound, such as described in US Patent No. 6,680,324 and US Patent No. 6,680,322.

The invention also provides A_1 adenosine receptor antagonist compounds with radioactive or non-radioactive labels. Such labelled compounds are useful as assay-type probes or conjugates, and may be used to obtain quantitative binding measurements of the A_1 adenosine receptor antagonist compounds. For the purposes of the invention, "assay-type probes" refers to those materials which are useful for enhancing the selectivity of the quantitative analysis of the A_1 adenosine receptor compounds of the

invention. Examples of such assay-type probes are described in U.S. Patent No. 5,248,770 to Jacobson et al., the disclosure of which is incorporated herein by reference in its entirety. The probes are highly useful in that they have little adverse effect on the affinity of the compounds of the present invention. Radioactive markers include, but are not limited to, an electric spin marker, a ^{19}F NMR probe, a radioactive ^{18}F isotope marker, a radioactive iodine marker (e.g., ^{125}I), a radioactive ^{3}H marker, tritium, and a complex of a metal atom or a metal ion and a chelating agent. An exemplary metal ion is a radioactive isotope of technetium or indium. An exemplary chelating agent is diethylene pentacetic anhydride.

Various non-radioactive materials may be used in labelling the present A_1 adenosine receptor compounds. Numerous examples are presented in U.S. Patent No. 5,248,770 to Jacobson et al. Biotin is used as a common non-radioactive label for such probes, as described in R.W. Old et al. *Principals of Gene Manipulation*, **4th ed**: 328-331 (1989). To facilitate labelling the compounds with biotin or any other appropriate material, a spacer component may be added to the compound according to an accepted method. Such a method is described in the Jacobson et al. '770 patent. Exemplary spacer components include, but are not limited to, an oligopeptide, triglycidyl, and N-hydroxysuccinimide ester.

Biotin may be bonded to any suitable linkage provided by substituents on the compound structure in accordance with any accepted and suitable technique. For example, referring to compound (I) as defined herein, biotin may be bonded to the hydroxy group on R_6 when the compound contains $(CH_2)_mOH$ at R_6 with m defined herein; to the amino group present on either of R_7 or R_8 when NH_2 is contained at these positions; or to the carboxyl group present when R_7 and R_8 are R_9COOH or $R_{10}COOH$ respectively, with R_9 and R_{10} defined herein. Additionally, the biotin may be bonded to a hydroxyl group present on R_8, when R_8 is $(CH_2)_sOH$ with s being defined herein. Biotin may also be bonded to R_7, when R_7 is $(CH_2)_tOH$ with t being defined herein. The biotin-labeled probes may be detected through appropriate and known analytical techniques.

Fluorescent dyes may also be employed as a non-radioactive labels and are applied to appropriate locations on the compounds of the invention. Such dyes include,

but are not limited to, tetramethylrhodamine, fluorescein isothiocyanate, and mixtures thereof. Other non-radioactive materials include for example, nitrobenzoxadiazole; 2,2,6,6-tetramethyl-piperindinyloxy-4-isothiocyanate; and mixtures thereof.

The invention is also directed to a pharmaceutical composition which includes the compound of the present invention and a pharmaceutically acceptable carrier.

The pharmaceutical composition is particularly useful in applications relating to organ preservation *in vivo* or *in situ*, perfusion of an isolated organ either removed or contained within the body (e.g., when an organ is transported for transplantation), cardiopulmonary bypass, perfusion of an extremity or limb, and the like. The compounds may be used in intra-articular, intra-thecal, gastrointestinal, and genital urinary applications, as well as in any cavity or lumen such as, for example, the thoracic cavity or ear canal.

The pharmaceutical composition may be employed, as an example, in oral dosage form as a liquid composition. Such liquid compositions can include suspension compositions or syrup compositions and can be prepared with such carriers as water; a saccharide such as sucrose, sorbitol, fructose, and the like; a glycol such as polyethyleneglycol, polypropyleneglycol, and the like; an oil such as sesame oil, olive oil, soybean oil, and the like; an antiseptic such as p-hydroxy- benzoic acid esters and the like; and a flavor component such as a fruit flavor or a mint flavor. The pharmaceutical composition may also be in the form of powder, pills, capsules, and tablets and can be prepared with various carriers. Suitable carriers include, but are not limited to, lactose, glucose, sucrose, mannitol, and the like; disintegrators such as starch, sodium alginate, and the like; binders such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, and the like; surfactants such as, for example, fatty acid esters; and plasticizers such as, for example, glycerins. The composition of the present invention is especially useful when applied sublingually. It should be noted that in the preparation of the tablets and capsules, a solid pharmaceutical carrier is used. Advantageously, the pharmaceutical composition may be used in the form of, for example, eye drops or an aerosol.

Other types of pharmaceutical compositions may be employed in the form of a suppository, a nasal spray, and an injectable solution. These compositions are prepared

using appropriate aqueous solutions which may include, but are not limited to, distilled water, and saline and buffer additives. Other components may be employed such as organic materials including neutral fatty bases. Additionally, the pharmaceutical composition may be utilized in a transdermal application.

Biopolymers may be used as carriers in the above pharmaceutical compositions. Exemplary biopolymers may include, for example, proteins, sugars, lipids or glycolipids. *See, e.g.*, C. Wilson, PCT Application WO 02/095391 (Published Nov. 22, 2002).

The A_1 receptor antagonists of the present invention are particularly useful as, for example, anti-allergenics, anti-inflammatory agents, CNS stimulants, diuretics, anti-asthmatics, cardiotonics, coronary vasodilators, and anti-tussives and as agents for the treatment of viral or retroviral infections and immune deficiency disorders such as acquired immunodefiency syndrome (AIDS).

The present invention also provides a method of treating A1 adenosine receptor related disorders, such disorders including but not limited to congestive heart failure, hypertension, such as systemic hypertension and pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, renal failure, Alzheimer's disease, depression, obesity, asthma, diabetes, cystic fibrosis, allergic conditions, including, but not limited to allergic rhinitis and anaphylactic shock, autoimmune disorders, inflammatory disorders, chronic obstructive pulmonary disorders, chronic cough, coronary artery disease, biliary colic, postoperative ileus, fibrosis, sclerosis, Adult Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), Severe Acute Respiratory Syndrome (SARS), septicemia, substance abuse, drug dependence, and Parkinson's disease.

The dosage of the active agent will depend upon the condition being treated, the age and condition of the subject, the route of administration, etc. In general the dosage can be determined in accordance with known techniques. In one embodiment the dosage of the active agent may, for example, be from 1 or 10 to 300 or 800 mg per adult subject.

Combination treatments. The compounds described herein may be used alone or in combination with other compounds for the treatment of the disorders described

herein, including but not limited to those compounds described in C. Wilson, PCT Application WO 03/103675, published Dec. 18, 2003.

Thus, according to other embodiments of the invention, the present invention relates to a method of treating A_1 adenosine receptor-related disorders, comprising concurrently administering:

(a) an A_1 adenosine receptor antagonist as described above, or a pharmaceutically acceptable salt thereof; with

(b) an additional active agent such as a compound selected from the group consisting of fluticasone propionate, salmeterol, theophylline, A_1 adenosine receptor antagonists, A_{2a} adenosine receptor agonists, A_{2b} adenosine receptor antagonists, A_3 adenosine receptor antagonists, P_{2y} purinoceptor agonists, and P_{2x} purinoceptor antagonists, and combinations thereof, in an amount effective to treat the A_1 adenosine receptor-related disorder.

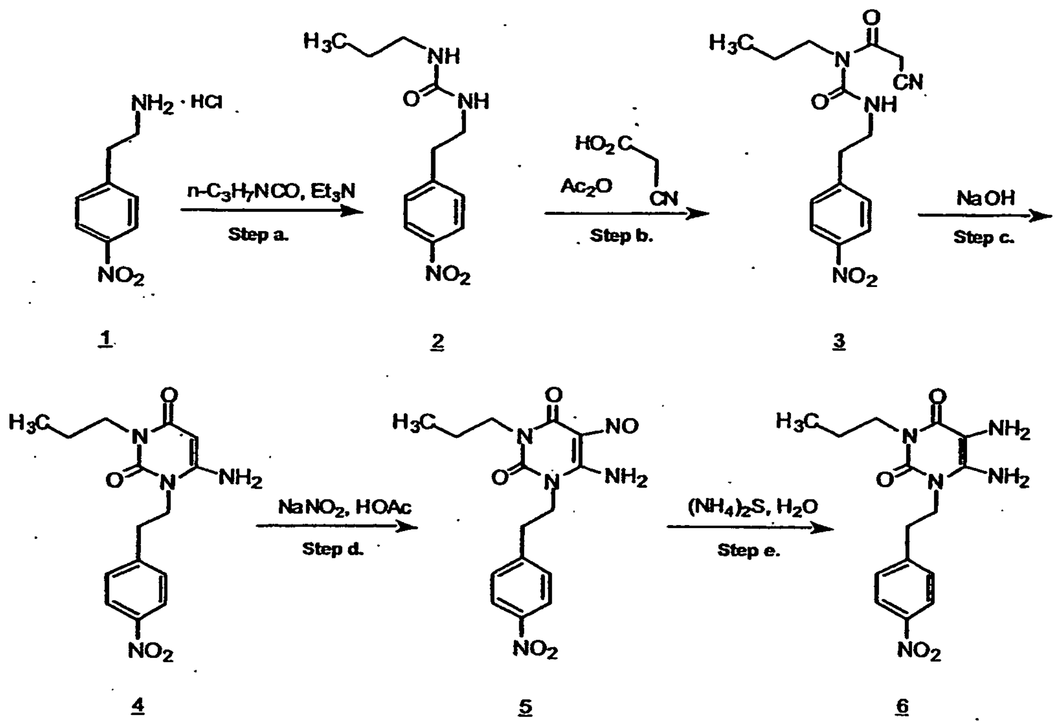
According to still other embodiments of the present invention, the present invention relates to a method of treating A_1 adenosine receptor-related disorders, comprising concurrently administering an A_1 adenosine receptor antagonist as described above with at least one additional active agent such as described above effective to treat A_1 adenosine receptor-related disorders, wherein the A_1 adenosine receptor-related disorder is as described above.

Administration of compounds in combination may be carried out in like manner as described above, with the active compound and the additional active agent being administered in the same or different carrier. Pharmaceutical formulations containing such combinations of active agents may also be prepared in like manner as described above.

The present invention is explained in greater detail in the following non-limiting Examples.

Example 1

Synthesis of 5,6-Diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6)



Step a: Conversion of 4-Nitrophenethylamine Hydrochloride (1) to 1-[2-(4-Nitrophenyl)ethyl]-1'-propylurea (2). To a slurry of 777 gm of 4-nitrophenethylamine hydrochloride (1) and 11.2 L of toluene was added slowly, 620 mL of triethylamine and this mixture was stirred for 30 min. at room temperature. To this suspension was then added slowly, 398 mL of n-propyl isocyanate, and the mixture was stirred overnight at room temperature to give a solid precipitate. The heterogeneous mixture was filtered and the isolated solids were washed with 1.5 L of toluene and then air dried. The 2.3 kg of crude product was stirred with 6 L of water to dissolve residual triethylamine hydrochloride. The solids were isolated by filtration and air dried. This material was dissolved in 4 L of absolute ethanol and 1 L of water was added to induce crystallization. The solids were filtered, washed with 2 L of 1:1 ethanol-water and air dried to yield a first crop of 880 gm of 1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (2). The recrystallization

mother liquors yielded an additional 39.8 gm of 1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (2).

Step b: Conversion of 1-[2-(4-Nitrophenyl)ethyl]-1'-propylurea (2) to 1'-Cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3). A thick mixture of 920 gm of 1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (2) and 1.0 L of acetic anhydride was stirred and warmed to ca. 50 degrees C. To this mixture was added 343.2 gm of cyanoacetic acid and 0.5 L of acetic anhydride and this homogeneous mixture was stirred at 80-85 degrees C for three hours. The mixture was cooled and concentrated under vacuum to remove acetic acid and residual acetic anhydride. The residue was triturated successively with 1.0 L portions of water, acetonitrile, toluene and ethyl acetate. The residue was then dried under vacuum to yield 1261 gm of a 2:1 mixture of 1'-cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3) and its undesired isomer 1-cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea. This material was dissolved in 2.2 L of hot ethyl acetate to which ca. 750 mL of hexanes were added to the cloud point and the mixture was allowed to cool to room temperature to induce crystallization. Filtration of the solid and air drying yielded 363 gm of 1'-cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3). If needed, additional recrystallizations from ethyl acetate-hexanes could be carried out to provide pure 1'-cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3).

Step c: Conversion of 1'-Cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3) to 6-Amino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (4). A mixture of ca. 2N sodium hydroxide was produced by dissolving 336 gm of solid sodium hydroxide in 4.2 L of water. To this warm solution was added, in portions, 312 gm of 1'-cyanoacetyl-1-[2-(4-nitrophenyl)ethyl]-1'-propylurea (3) and the mixture was stirred for 1 hour at 80 degrees C, then was cooled to room temperature with stirring to induce crystallization. The solids were isolated by filtration, washed with four 500 mL portions of water and vacuum dried at 65 degrees C to yield 232 gm of crude 6-amino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (4).

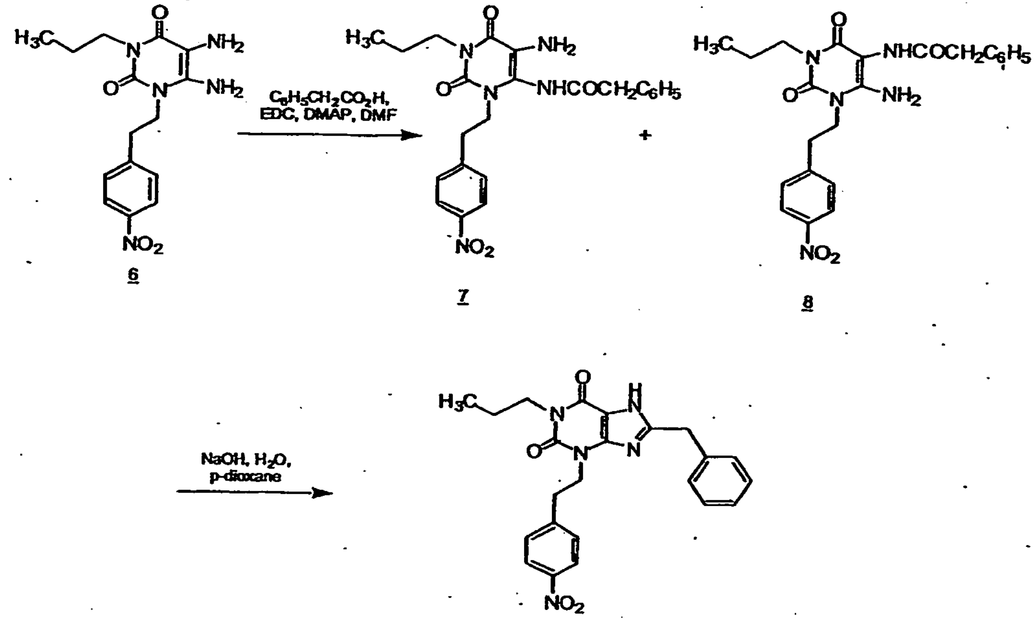
Step d: Conversion of 6-Amino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (4) to 6-Amino-5-nitroso-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (5). To a solution of 232 gm of crude 6-amino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (4), 4.0 L of water and ca.

2.0 L of ethanol at 80 degrees C was added 55.3 gm of sodium nitrite in one portion, followed by the dropwise addition of 100 mL of glacial acetic acid. After stirring at 80 degrees C for 20 minutes the mixture was allowed to cool to near room temperature, then was chilled in an ice bath to effect crystallization. The solids were isolated by filtration, washed with two 1.0 L portions of water and dried under vacuum to yield 244 gm of purple colored 6-amino-5-nitroso-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (5).

Step e: Conversion of 6-Amino-5-nitroso-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (5) to 5,6-Diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6). A mixture of 243 gm of 6-amino-5-nitroso-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (5), and 2.1 L of water was heated to reflux and 528 mL of a 50% aqueous solution of ammonium sulfide was added with stirring to control foaming. The dark solution was stirred at 90-100 degrees C for 30 min. and allowed to cool with stirring for 1.5 hours. The mixture was then chilled in an ice bath to fully effect crystallization. The solids were isolated by filtration, washed with three 500 mL portions of water and dried under vacuum to yield 219 gm of a dark solid. This material was recrystallized from 1.0 L of acetonitrile to yield two crops totaling 169.5 gm of 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6).

Example 2

Synthesis of 8-Benzyl-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine (9)

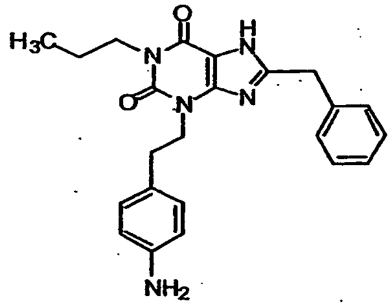


A solution of 44.9 gm of phenylacetic acid in 630 mL of dimethylformamide (DMF) was chilled in an ice water bath and 63.38 gm of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was added followed by 5.24 gm of 4-dimethylaminopyridine (DMAP). This mixture was stirred at ca. 4 degrees C for 30 minutes and 100 gm of 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) was added in one portion. This mixture was stirred for 60 hr at room temperature. The dark homogeneous solution was poured into 700 mL of ice water with stirring to effect precipitation. The solids were isolated by filtration, washed with three 100 mL portions of water and dried under vacuum to yield 103 gm of a mixture of 5-amino-1-[2-(4-nitrophenyl)ethyl]-6-phenacetoamino-3-propyluracil (7) and 6-amino-1-[2-(4-nitrophenyl)ethyl]-5-phenacetoamino-3-propyluracil (8) intermediates. These solids were dissolved in 450 mL of p-dioxane, 600 mL of 2N aqueous sodium hydroxide was added and the mixture was heated at reflux for one hr. The solution was then chilled in an ice water bath and the pH adjused to pH 4 with ca. 100 mL of concentrated hydrochloric acid to yield a precipitate. The solids were isolated by filtration, washed with three 100 mL

portions of water and dried under vacuum to yield 82 gm of an orange solid. Recrystallization from hot ethyl acetate afforded 58.0 gm of 8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine (9).

Example 3

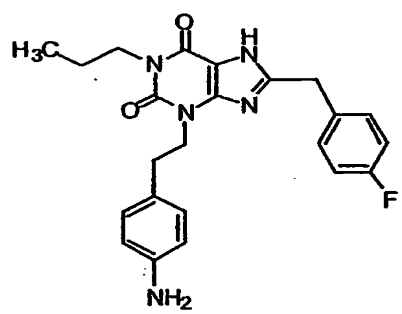
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-propylxanthine



By methods well known in the art, 8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine (9) is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-propylxanthine.

Example 4

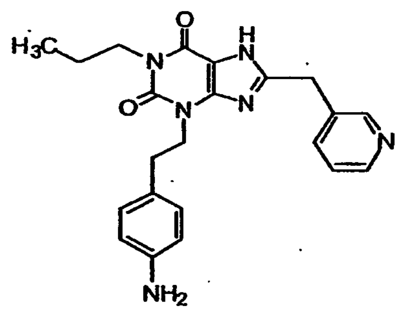
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-8-(4-fluorobenzyl)-1-propylxanthine



By the method of Example 2, 4-fluorophenylacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 8-(4-fluorobenzyl)-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine. By methods well known in the art, 8-(4-fluorobenzyl)-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-8-(4-fluorobenzyl)-1-propylxanthine.

Example 5

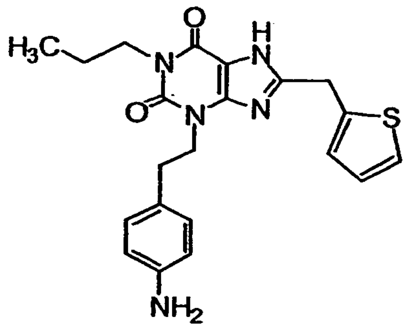
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine



By the method of Example 2, 3-pyridylacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine. By methods well known in the art, 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine.

Example 6

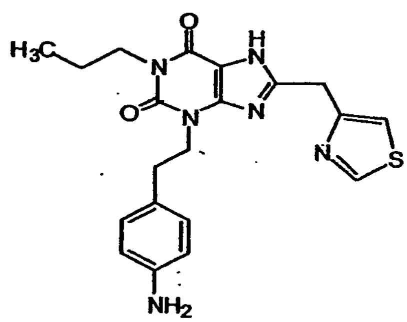
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine



By the method of Example 2, 2-thiopheneacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine. By methods well known in the art, 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine.

Example 7

Synthesis of 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(4-thiazolyl)methyl]xanthine

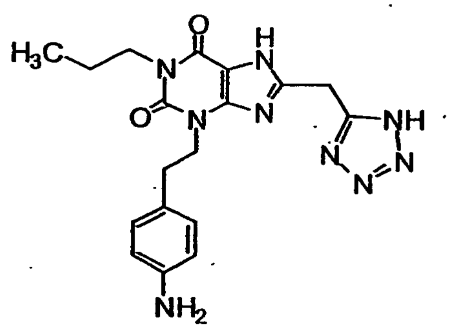


By the method of Example 2, 4-thiazolylacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(4-thiazolyl)methyl]xanthine. By methods well known in the art, 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(4-thiazolyl)methyl]xanthine is reduced with hydrazine

hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(4-thiazolyl)methyl]xanthine.

Example 8

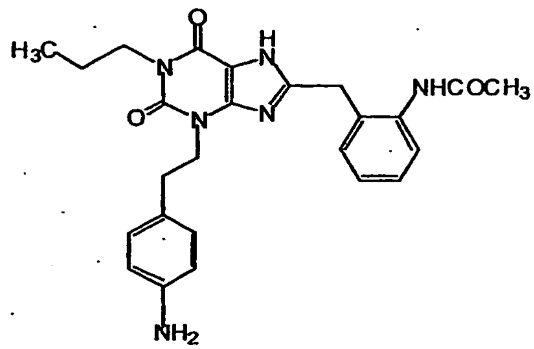
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine



By the method of Example 2, 1*H*-tetrazole-5-acetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine. By methods well known in the art, 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine.

Example 9

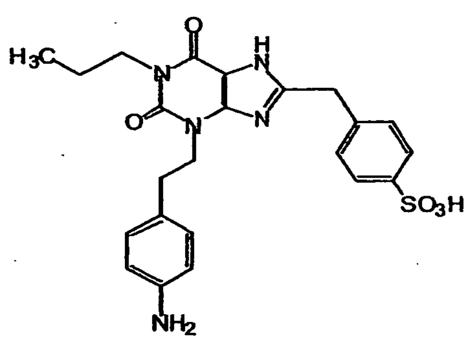
Synthesis of 8-(2-Acetaminobenzyl)-3-[2-(4-aminophenyl)ethyl]-1-propylxanthine



By the method of Example 2, 2-(acetamino)phenylacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 8-(2-acetaminobenzyl)-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine. By methods well known in the art, 8-(2-acetaminobenzyl)-3-[2-(4-nitrophenyl)ethyl]-1-propylxanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 8-(2-acetaminobenzyl)-3-[2-(4-aminophenyl)ethyl]-1-propylxanthine.

Example 10

Synthesis of 3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine

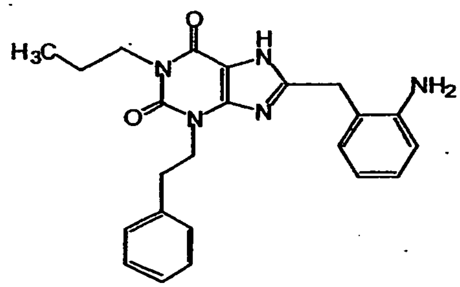


By the method of Example 2, 4-sulfonoxyphenylacetic acid is reacted with 5,6-diamino-1-[2-(4-nitrophenyl)ethyl]-3-propyluracil (6) to yield 3-[2-(4-nitrophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine. By methods well known in the art, 3-[2-(4-

nitrophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine.

Example 11

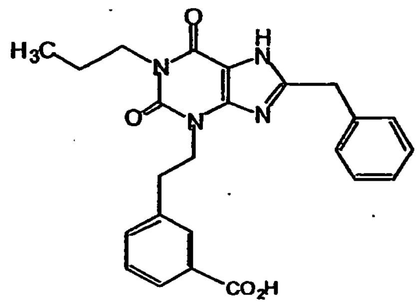
Synthesis of 8-(2-Aminobenzyl)-3-(2-phenylethyl)-1-propylxanthine



By the method of Example 2, 2-(acetamino)phenylacetic acid is reacted with 5,6-diamino-1-(2-phenylethyl)-3-propyluracil to yield 8-(2-acetaminobenzyl)-3-(2-phenylethyl)-1-propylxanthine. By methods well known in the art, 8-(2-acetaminobenzyl)-3-(2-phenylethyl)-1-propylxanthine is hydrolyzed with base to yield 8-(2-aminobenzyl)-3-(2-phenylethyl)-1-propylxanthine. In turn, 5,6-diamino-1-(2-(phenylethyl)-3-propyluracil is made by the synthetic methods of Example 1, starting with phenethylamine hydrochloride.

Example 12

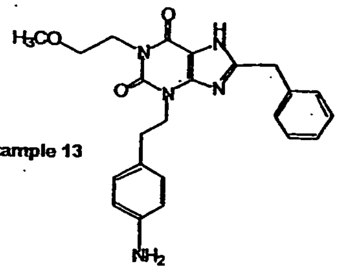
Synthesis of 8-Benzyl-3-[2-(3-carboxyphenyl)ethyl]-1-propylxanthine



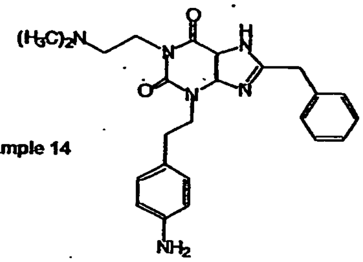
By the method of Example 2, phenylacetic acid is reacted with 5,6-diamino-1-[2-(3-carboxyphenyl)ethyl]-3-propyluracil to yield 8-benzyl-3-[2-(3-carboxyphenyl)ethyl]-1-propylxanthine. In turn, 5,6-diamino-1-[2-(3-carboxyphenyl)ethyl]-3-propyluracil is made by the synthetic methods of Example 1, starting with 3-carboxyphenethylamine.

Examples 13-18

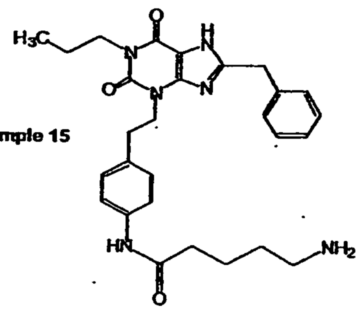
Examples 13-18 describe the synthesis of the following compounds:



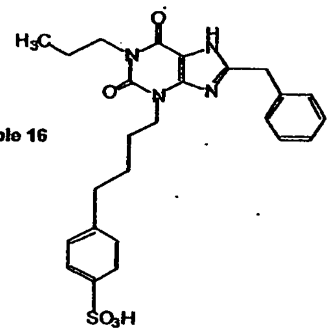
Example 13



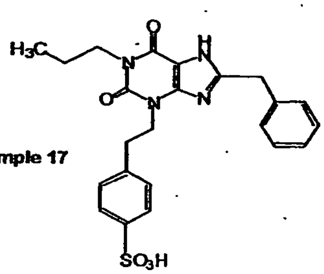
Example 14



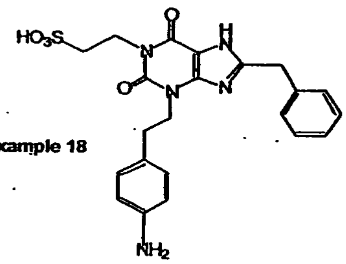
Example 15



Example 16



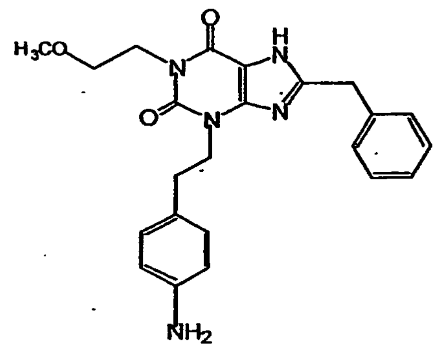
Example 17



Example 18

Example 13

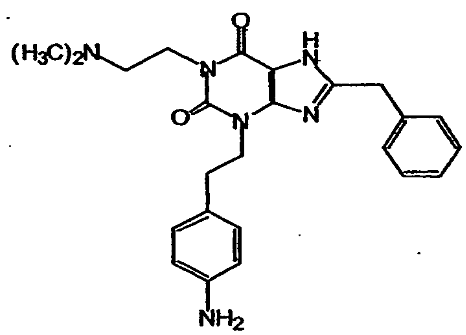
Synthesis of 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine



By methods well known in the art 3-methoxypropyl isocyanate is converted into 8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-(3-methoxypropyl)xanthine, which in turn, is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine.

Example 14

Synthesis of 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-dimethylamino)propylxanthine

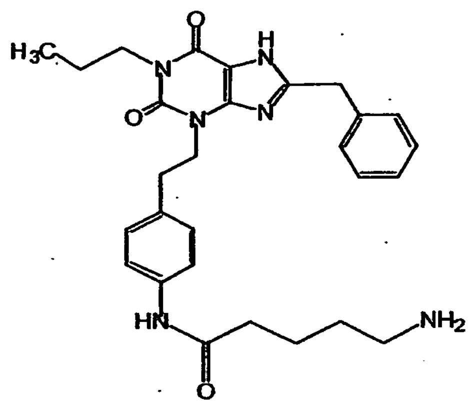


By methods well known in the art 3-dimethylaminopropyl isocyanate is converted into 8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-(3-dimethylaminopropyl)xanthine, which in turn, is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium

catalyst to yield 3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-(3-dimethylaminopropyl) xanthine.

Example 15

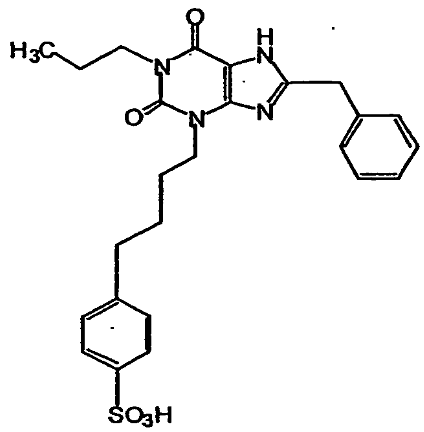
Synthesis of 3-[2-[4-(6-Aminohexanoyl)aminophenyl]ethyl] -8-benzyl-1-propylxanthine



By methods well known in the art, 3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-propylxanthine is reacted with 6-aminohexanoic acid and a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) to yield 3-[2-[4-(6-aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine.

Example 16

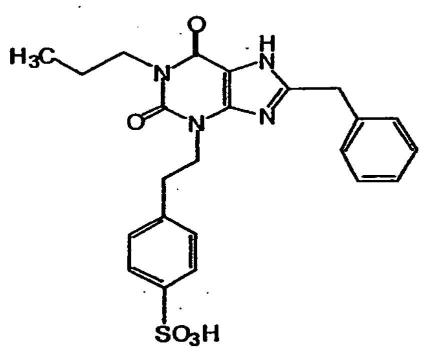
Synthesis of 8-Benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine



By the method of Example 2, phenylacetic acid is reacted with 5,6-diamino-1-[4-(4-sulfonoxyphenyl)butyl]-3-propyluracil to yield 8-benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine. In turn, 5,6-diamino-3-propyl-1-[4-(4-sulfonoxyphenyl)butyl]-3-uracil is made by the synthetic methods of Example 1, starting with n-propyl isocyanate and 4-(4-sulfonoxyphenyl)butylamine.

Example 17

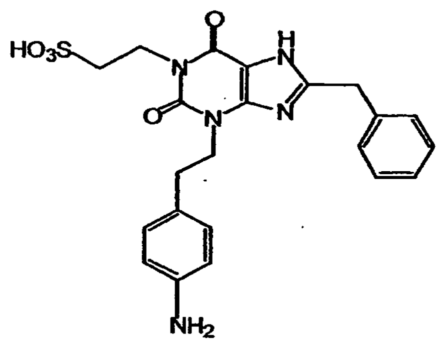
Synthesis of 8-Benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine



By the method of Example 2, phenylacetic acid is reacted with 5,6-diamino-1-[2-(4-sulfonoxyphenyl)ethyl]-3-propyluracil to yield 8-benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine. In turn, 5,6-diamino-1-[2-(4-sulfonoxyphenyl)ethyl]-3-propyluracil is made by the synthetic methods of Example 1, starting with 4-sulfonoxyphenethylamine.

Example 18

Synthesis of 3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine

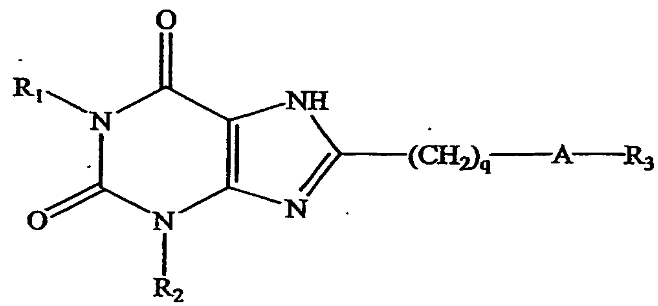


By methods well known in the art a protected 3-sulfonoxypropyl isocyanate is converted into 8-benzyl-3-[2-(4-nitrophenyl)ethyl]-1-(3-sulfonoxypropyl)xanthine, which in turn, is reduced with hydrazine hydrate or hydrogen gas in the presence of a palladium catalyst to yield 3-[2-(4-aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine.

In the specification above, there have been disclosed typical preferred embodiments of the invention and, although specific terms are employed, they are used in a generic and descriptive sense only and not for purposes of limitation of the scope of the invention being set forth in the following claims.

THAT WHICH IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein:

A is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O, and S;

R_1 or R_2 is of the formula (i):

$$(CH_2)_r—A'—R_4 \qquad \text{(i)}$$

wherein:

A' is a 5- or 6-membered aromatic or heteroaromatic ring containing 0 to 4 heteroatoms selected from the group consisting of N, O, and S;

r is an integer ranging from 1 to 20;

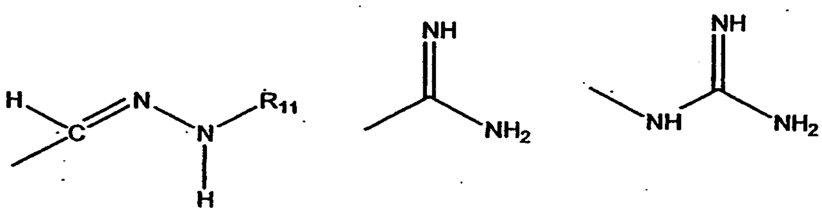
R_4 is selected from the group consisting of H; NH_2; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; $R_{14}COOH$, wherein R_{14} is an alkyl or alkylidene group having 1 to 8 carbon atoms, halo, NHR_8, NR_8R_9, $NHCOR_8$, NR_8COR_9, SO_3H and PO_3H_2;

R_3 is selected from the group consisting of H, NH_2, $R_{15}COOH$, wherein R_{15} is an alkyl or alkylidene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an

integer ranging from 1 to 8; halo, NHR_8, NR_8R_9, $NHCOR_8$, NR_8COR_9, SO_3H and PO_3H_2;

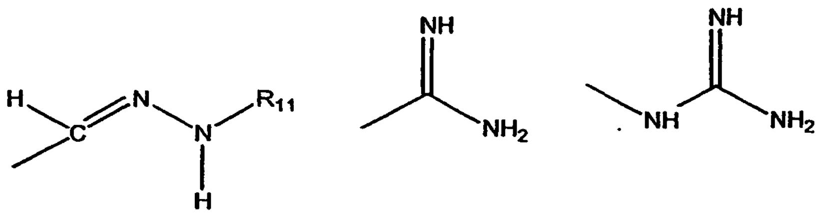
q is an integer ranging from 1 to 8;

or R_1 is a C_1-C_8 alkanyl group, C_2-C_8-alkenyl- or C2-C8 -alkynyl- group which is optionally substituted by -CN, -$CH_2NR_6R_7OH$, -OR_8, -NR_6R_7, -$NHCOR_8$, -$NHCONR_6R_7$, halogen, -$OCOR_8$, -OCH_2COOH, -OCH_2COOR_8, -SO_2R_5, -S-R_5, -NHCONH phenyl, -OCH_2-$CONR_6R_7$, -OCH_2CH_2OH, -SO_2-CH_2-CH_2-O-COR_8, -OCH_2-CH_2-NR_6R_7, -SO_2-CH_2-CH_2-OH, -$CONHSO_2R_8$, -$CH_2CONHSO_2R_8$, -$OCH_2CH_2OR_8$, -COOH, –$COOR_8$, -$CONR_6R_7$, -CHO, -SR_8, -SOR_8, -SO_2R_8, -SO_3H, -PO_3H_2, -$SO_2NR_6R_7$, -OCH_2-CH_2OCOR_8, -CH=NOH, -CH=NOR_8, -COR_9, -CH(OH)R_9, -CH$(OR_8)_2$, -CH=CH-R_{10}, -$OCONR_6R_7$,



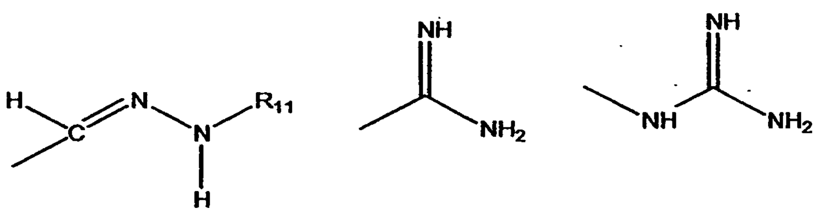
or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or

denotes phenyl-C_1-C_6-alkylene, phenyl-C_2-C_6-alkenylene or phenyl-C_2-C_6-alkynylene, in which the phenyl ring is optionally substituted, either directly or via a C_1-C_4-alkylene group, with one or more of the following groups: -C_1-C_3-alkyl, -CN, -$CH_2NR_6R_7$, -NO_2, -OH, -OR_8, -CH_2-NH-SO_2-R_8, -$NHCOR_8$, -$NHCONR_6R_7$, halogen, -$OCOR_8$, -OCH_2COOH, -OCH_2COOR_8, -CH_2OCOR_8, -SO_2R_5, -OCH_2-$CONR_6R_7$, -OCH_2CH_2OH, -OCH_2-CH_2-NR_6R_7, -$CONHSO_2R_8$, -$OCH_2CH_2OR_8$, -COOH, -$COOR_8$, -CF_3, cyclopropyl, -$CONR_6R_7$, -CH_2OH, -CH_2OR_8, -CHO, -SR_8, –SOR_8, -SO_2R_8, -SO_3H, -PO_3H_2, -$SO_2NR_6R_7$, -OCH_2-CH_2OCOR_8, -CH=NOH, -CH=NOR_8, -COR_9, -CH(OH)R_9, -CH$(OR_8)_2$, -$NHCOOR_8$, -$CH_2CONHSO_2R_8$, -CH=CH-R_{10}, -$OCONR_6R_7$, -CH_2-O-$CONR_6R_7$, -CH_2-CH_2-O-$CONR_6R_7$,



or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or

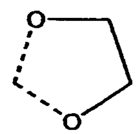
denotes C_3-C_7-cycloalkyl-C_1-C_6-alkylene-, C_3-C_7-cycloalkyl-C_2-C_6-alkenylene-, C_3-C_7 -cycloalkyl-C_2-C_6-alkynylene-, in which the cycloalkyl group may optionally be substituted, either directly or via a C_{1-4}-alkylene group, by -CN, -$CH_2NR_6R_7$, =O, -OH, -OR_8, -NR_6R_7, -$NHCOR_8$, -$NHCONR_6R_7$, halogen, —$OCOR_8$, -OCH_2COOH, -OCH_2COOR_8, -CH_2OCOR_8, -SO_2R_5, -$OCH_2CONR_6R_7$, -OCH_2CH_2OH, -OCH_2-CH_2-NR_6R_7, -$OCH_2CH_2OR_8$, -COOH, -$COOR_8$, -$CONR_6R_7$, -CH_2OH, -CH_2OR_8, -CHO, -SR_8, -SOR_8, -SO_2R_8, -SO_3H, -PO_3H_2, -$SO_2NR_6R_7$, -OCH_2-CH_2-$OCOR_8$, -CH=NOH, -CH=NOR_8, -COR_9, -CH(OH)R_9, -$CONHSO_2R_8$, -CH$(OR_8)_2$, -$NHCOOR_8$, -CH=CH-R_{10}, -$OCONR_6R_7$, -CH_2-O-$CONR_6R_7$7, -CH_2-CH_2-O-$CONR_6R_7$,



or by 1,3-dioxolane or 1,3-dioxane which is optionally mono- or polysubstituted by methyl; or

denotes a group of the formula A-C_1-C_6-alkylene-, A-CONH-C_1-C_6-alkylene-, A-CONH-C_2 –C_6-alkenylene-, A-CONH-C_2-C_6-alkynylene-, A-NH-CO-C_1-C_6-alkylene, A-NH-CO-C_2-C_6-alkenylene, A-NH-CO-C_2-C_6 alkynylene, A-C_2-C_6-alkenylene- or A-C_2 – C_6-alkynylene, wherein A is a C- or N-linked 5- or 6-membered heterocyclic ring, 5- or 6- membered aromatic ring, or 5-or 6- membered heteroaromatic ring which contains

nitrogen, oxygen or sulphur as heteroatoms and may optionally be mono- or polysubstituted, by C_1-C_4-alkyl, halogen, $-OR_8$, -CN, $-NO_2$, $-NH_2$, $-CH_2NR_6R_7$, -OH, =O, a ketal, -COOH, $-SO_3H$, $-PO_3H_2$, $-COOR_8$, $-CONR_6R_7$, $-COR_9$, $-SO_2-R_8$, $-CONR_6R_7$ or



R_5 denotes C_1-C_4-alkyl, optionally substituted by OH, $OCOR_8$, NH_2, NR_6R_7 or $NHCOR_8$,

R_6 denotes hydrogen, an optionally substituted C_{3-6}-cycloalkyl group, a branched or unbranched alkyl-, alkenyl- or alkynyl group having up to 10 carbon atoms, preferably a C_1-C_4-alkyl group, which may optionally be substituted by hydroxy, phenyl, substituted phenyl, amino, substituted amino, C_1 to C_8, or it denotes $-(CH_2)_m-NHCOOR_8$ wherein m=1, 2, 3 or 4;

R_7 denotes hydrogen, an optionally substituted C_{3-6}-cycloalkyl group, a branched or unbranched alkyl-, alkenyl- or alkynyl group having up to 10 carbon atoms, which may optionally be substituted by hydroxy, phenyl, substituted phenyl, amino, substituted amino, C_1 to C_8, -or it denotes $-(CH_2)_m-NHCOOR_8$ wherein m=1, 2, 3 or 4; or R_6 and R_7 together with the nitrogen atom form a saturated or unsaturated 5- or 6-membered ring which may contain as heteroatoms nitrogen, oxygen or sulphur, while the heterocyclic ring may be substituted by a branched or unbranched C_{1-4}-alkyl group, or may carry one of the following groups: $-(CH_2)_n-NH_2$, =O, a ketal - preferably $-O-CH_2-CH_2-O-$, $-(CH_2)_n-NH-C_1-C_4$-alkyl, $-(CH_2)_n-N(C_1-C_8$-alkyl), $-(CH_2)_n-NHCOOR_8$, (n=2, 3, 4,), halogen, $-OR_8$, -CN, $-NO_2$, $-NH_2$, $-CH_2NR_6R_7$, -OH, -COOH, $-SO_3H$, $-PO_3H_2$, $-COOR_8$, $-CONR_6R_7$, $-SO_2R_8$,

R_8 denotes hydrogen, C_1-C_8-alkyl or C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted with CO_2H, a benzyl- or phenyl- group, which is optionally mono- or polysubstituted by OCH_3;

R_9 denotes C_1-C_8-alkyl or C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted with CO_2H, optionally substituted phenyl, optionally substituted benzyl, C_3-C_6-cycloalkyl, and

R_{10} denotes $-COOR_8$, $-CH_2OR_8$, $-CONR_6R_7$, hydrogen, C_1-C_3-alkyl, optionally substituted phenyl, $-CH_2NR_6R_7$;

and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

2. The compound of claim 1, wherein at least one of R_3 and R_4 is independently selected from the group consisting of SO_3H and PO_3H_2.

3. The compound of claim 1, wherein R_1 or R_2 is a C_1-C_8 alkanyl group, C_2-C_8-alkenyl group or C_2-C_8 alkynyl group which is optionally substituted by NR_6R_7, $-SO_3H$, or $-PO_3H_2$.

4. The compound of claim 1, wherein A is phenyl.

5. The compound of claim 1, wherein A' is phenyl.

6. The compound of claim 1, wherein:

R_1 is a C_1-C_8 alkanyl group, C_2-C_8-alkenyl group or C_2-C_8 alkynyl group which is optionally substituted by NR_6R_7 or $-SO_3H$;

A is phenyl; and

A' is phenyl.

7. The compound of claim 6, wherein at least one of R_3 and R_4 is independently selected from the group consisting of SO_3H and PO_3H_2.

8. The compound of claim 1, wherein said compound is selected from the group consisting of:

3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-propylxanthine;

3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine;
3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(4-thiazolyl)methyl]xanthine;
3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-dimethylamino)propylxanthine;
3-[2-[4-(6-Aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine;
8-Benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine;
8-Benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine;
and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

9. The compound of claim 1, wherein said compound is selected from the group consisting of:

8-Benzyl-1-propyl-3-[4-(4-sulfonoxyphenyl)butyl]xanthine;
8-Benzyl-1-propyl-3-[2-(4-sulfonoxyphenyl)ethyl]xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-sulfonoxypropyl)xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-(4-fluorobenzyl)-1-propylxanthine;
3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(thiophen-2-yl)methyl]xanthine;
3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(1*H*-tetrazol-5-yl)methyl]xanthine;
8-(2-Acetaminobenzyl)-3-[2-(4-aminophenyl)ethyl]-1-propylxanthine;
8-(2-Aminobenzyl)-3-(2-phenylethyl)-1-propylxanthine;
8-Benzyl-3-[2-(3-carboxyphenyl)ethyl]-1-propylxanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(8-sulfonoxyoctyl)xanthine;
3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(5-sulfonoxypentyl)xanthine;
and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

10. The compound of claim 1, wherein said compound is selected from the group consisting of:

3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-propylxanthine;
3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-[(3-pyridyl)methyl]xanthine;

3-[2-(4-Aminophenyl)ethyl]-1-propyl-8-(4-sulfonoxybenzyl)xanthine;

3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-methoxypropyl)xanthine;

3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(3-dimethylamino)propylxanthine;

3-[2-[4-(6-Aminohexanoyl)aminophenyl]ethyl]-8-benzyl-1-propylxanthine;

and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

11. The compound of claim 1, wherein said compound is selected from the group consisting of:

3-[2-(4-Aminophenyl)ethyl]-8-benzyl-1-(5-sulfonoxypentyl)xanthine;

and pharmaceutically acceptable salts, hydrates and prodrugs thereof.

12. A composition comprising a compound of claim 1 in a pharmaceutically acceptable carrier.